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Oral contraceptive progestins and angiotensin-dependent control of the renal circulation in humans

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Abstract

Oral contraceptive (OC) use is associated with increased intra-renal renin-angiotensin-aldosterone system (RAA System) activity and risk of nephropathy, though the contribution of progestins contained in the OC in the regulation of angiotensin-dependent control of the renal circulation has not been elucidated. Eighteen OC users (8 non-diabetic, 10 Type 1 diabetic) were studied in high salt balance, a state of maximal RAA System suppression. Progestational and androgenic activity of the progestin in each OC was standardized to that of the reference progestin norethindrone. Renal plasma flow (RPF) was measured by paraaminohippurate clearance at baseline and in response to angiotensin converting enzyme (ACE)-inhibition. There was a positive correlation between OC progestational activity and the RPF response to ACE-inhibition ($r=0.52$, $p=0.03$). Similar results were noted with OC androgenic activity ($r=0.54$, $p=0.02$). On subgroup analysis, only non-diabetic subjects showed an association between progestational activity and angiotensin-dependent control of the renal circulation ($r=0.71$, $p=0.05$ non-diabetic; $r=0.14$, $p=0.7$ diabetic; $p=0.07$ between groups). Similar results were noted with respect to androgenic activity ($r=0.88$, $p=0.005$ non-diabetic; $r=-0.33$, $p=0.3$ diabetic; $p=0.002$ between groups). Our results suggest that the OC progestin component is a significant influence on the degree of angiotensin-dependent control of the renal circulation, though these findings may not apply to women with diabetes.

Keywords

Progestational activity; Androgenic activity; Renal plasma flow; Female Oral contraceptive

Introduction

Oral contraceptive (OC) use has been associated with increased intrarenal rennin-angiotensin-aldosterone system (RAA System) activity^{1–3} and risk of nephropathy,^{4–6} though the relative individual contributions of the progestin and estrogen components in the OC have not been elucidated. While most OCs contain ethinyl estradiol as the synthetic

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Disclosures

None.

estrogen component, they contain different progestins which vary in terms of their chemical composition, potency and formulary dose. As a result, synthetic progestins have varying levels of progestational and androgenic activity,⁷ and these sex hormones have each been shown to affect RAA System activity.^{8–10}

The importance of the type of progestin contained in hormonal preparations has been previously highlighted.^{11, 12} Studies have suggested a link between adverse cardiac,¹³ vascular,¹⁴ and thrombotic¹⁵ events depending on the type of progestin exposure, and that the type of progestin in a hormonal preparation may play a role in attenuating the vascular effects of estrogen.^{11, 16} A recent study suggests that OCs containing some newer generation progestins are associated with worsening blood pressure, urinary albumin excretion and renal function;¹⁷ though the exact mechanism remains unclear, animal studies have shown an inverse association between exogenous progestin administration and the pressor response to Ang II,^{18, 19} suggesting a relationship between progestins and activity of the RAA System. While it is clear that ingestion of OCs is associated with an altered state of intrarenal RAA System activity in both non-diabetic^{2, 3, 6} and diabetic⁶ women, the influence of the OC progestin component on the degree of angiotensin-dependent control of the renal circulation in humans is not known. Furthermore, as we have previously shown that OC use further enhances the RAA System activation that occurs in diabetes,⁶ we sought to determine whether the progestin component in the OC influences the response to ACE-inhibition in not only healthy subjects, but also in women with diabetes.

Given the link between progestins and altered RAA System activity, and the strong association between increased renal RAA System activity and OC use, we hypothesized that the level of progestational and androgenic activity of the progestin in the OC was a determinant of the degree of angiotensin-dependent control of the renal circulation in humans. Thus, we examined renal hemodynamic function, both at baseline and in response to the angiotensin converting enzyme (ACE)-inhibitor captopril in 18 women stratified according to diabetic status, as a function of OC progestational and androgenic activity.

Materials and Methods

Subjects

Eighteen female OC users (8 non-diabetic, 10 Type 1 diabetes) participated in the study. Subjects completed an initial medical history, physical examination, electrocardiogram, and laboratory screening. No subject was taking medication other than OCs and insulin. Subjects were questioned as to the specific OC they were ingesting, from which the dosage of ethinyl estradiol and the type and amount of progestin was derived. If the OC was a multiphasic formulation, an average daily concentration was derived unless the exact dosage at the time of the study was known. The progestational and androgenic activity of each progestin was expressed as receptor binding affinity (RBA) and standardized to the activity of the progestin norethindrone, as has been done previously in human studies.²⁰ All subjects gave written informed consent. The study protocol was approved by the local Institutional Review Board.

Protocol

Subjects consumed >200mmol sodium/day for 4 days before the study. Sodium, creatinine, and protein excretion were measured from a 24h urine collection; no data were excluded because of dietary noncompliance. Subjects were studied in the supine position after an 8h fast. At 8:00 A.M., an intravenous catheter was placed in each arm (for infusion and blood sampling). Fasting plasma glucose concentrations were measured at the start of the study. Diabetic subjects received intravenous insulin at 0.015units/kg/h, titrated to maintain blood

glucose between 80–150mg/dl (4.4–8.3mmol/L). Blood pressure (BP) was recorded every 15min by an automatic recording device (Dinamap; Critikon, Tampa, FL). A loading dose of 8mg/kg of para-aminohippurate (PAH), followed by a constant infusion of PAH at 12mg/min was given for 90min to establish baseline renal hemodynamic measurements, followed by 25mg captopril taken orally. PAH clearance and plasma renin activity were measured at baseline and up to 240min after captopril ingestion.

Analytical methods

Renal clearance was assessed with PAH (Clinalfa, Läufelfingen, Switzerland) as previously described.²¹ Serum PAH was measured by an autoanalyzer. Plasma renin activity (PRA) was assayed by radioimmunoassay.²¹

Statistical analysis

The primary analysis tested associations between OC progestational and androgenic activity and change in RPF in response to ACE-inhibition. Study subject baseline and response to captopril measures were compared using nonparametric methods. The chi-square test was used to compare frequencies. Renal vascular resistance (RVR) was calculated using the equation $RVR = [(mean\ arterial\ BP - 12) \times 723 / RPF]$. Statistical analyses were performed using Stata (version 9.0; Stata, College Station, TX) with two-tailed significance levels of 0.05.

Results

Baseline characteristics

All subjects were normotensive and none were obese (Table 1). There were no significant differences in baseline characteristics between non-diabetic and diabetic subjects. The OCs ingested by all subjects contained progestins structurally related to testosterone. No subjects were ingesting OCs containing progesterone-derived progestins (Table 2).

Renal and Systemic hemodynamic responses to captopril

As anticipated, all subjects demonstrated a renal vasodilatory response to ACE-inhibition ($p=0.0005$), which did not differ by diabetic status ($p=0.6$) (Table 3). While no association was observed between the dose of ethinyl estradiol and the RPF response to captopril ($r=-0.14$, $p=0.6$), there was a positive correlation between increasing OC progestational activity and the RPF response to ACE-inhibition ($r=0.52$, $p=0.03$) (Figure 1). Similar results were noted with increasing OC androgenic activity ($r=0.54$, $p=0.02$) (Figure 2). A multiplicative effect of increased progestational and androgenic activity on the RPF response to ACE-inhibition was observed ($p=0.01$). On sub-group analysis, only non-diabetic subjects showed an association between increasing progestational activity of the progestin component of the OC and angiotensin-dependent control of the renal circulation ($r=0.71$, $p=0.05$ for non-diabetic subjects; $r=0.14$, $p=0.7$ for diabetic subjects; $p=0.07$ for difference between groups). Similar results were noted with respect to androgenic activity of the OC progestin component ($r=0.88$, $p=0.005$ for non-diabetic subjects, $r=-0.33$, $p=0.3$ for diabetic subjects; $p=0.002$ for difference between groups) (Figure 3).

Mean arterial pressure decreased in response to ACE-inhibition in all subjects, ($p=0.004$), and the decrease in MAP was similar between non-diabetic and diabetic subjects ($p=0.2$). Neither OC progestational nor androgenic activity influenced the MAP response to captopril ($p=0.5$ for OC progestational activity, $p=0.4$ for OC androgenic activity). There was no correlation between the change in MAP and the change in RPF in response to ACE-inhibition ($p=0.1$).

Renal vascular resistance (RVR) decreased significantly in all subjects with ACE-inhibition ($p=0.003$ for all subjects, $p=0.03$ for non-diabetic subjects, $p=0.005$ for diabetic subjects). A negative correlation was noted between change in RVR and both progestational activity ($r=-0.49$, $p=0.04$ all subjects; $r=-0.58$, $p=0.1$ non-diabetic subjects; $r=-0.67$, $p=0.03$ diabetic subjects), and androgenic activity ($r=-0.49$, $p=0.04$ all subjects; $r=-0.53$, $p=0.2$ non-diabetic subjects; $r=-0.57$, $p=0.08$ diabetic subjects). The enhanced renovascular response to captopril in OC users with higher progestational or androgenic activity was not reflected in the PRA, thus suggesting a difference in local tissue RAA System activity, such as in the kidney.

Discussion

In this study of 18 women ingesting OCs while in high salt balance, a state of maximal RAA System suppression, a positive correlation between increasing OC progestational activity and RPF response to ACE-inhibition was observed. Similarly, greater OC androgenic activity was also positively associated with the RPF response to captopril, suggesting that increasing progestational and androgenic activity in the OC is associated with enhanced angiotensin-dependent control of the renal circulation, and thus a potential increase in the risk of nephropathy.

Many factors are associated with RAA System activation. Diabetes^{22, 23} and acute hyperglycemia are both linked to an activated renal RAA System in healthy^{24, 25} and diabetic subjects,²⁶ though all of our subjects were euglycemic. Nephron loss ultimately results in increased Ang II production,²⁷ but all subjects had baseline renal hemodynamics in the normal range. A positive correlation between body mass index and the renal response to ACE-inhibition has been shown,²⁸ but all subjects were non-obese. While smoking is hypothesized to lead to increased Ang II production,²⁹ premenopausal women appear to be least affected by the adverse renal effects of smoking.²⁹

Progestin composition and thereby its inherent progestational and androgenic activity vary widely amongst the different OC formulations and thus it may not be possible to completely separate the progestational and androgenic effects of a particular progestin. Furthermore, the evaluation of progestational and androgenic activity of the OC progestin in humans is challenging, but can include measuring the progestin affinity for and binding to the progesterone (PR) and androgen receptor (AR), its effect on sex hormone binding globulin and free testosterone levels, and its degree of binding to sex hormone binding globulin.^{30–33} However, all progestins bind to the progestin receptor³⁴ and exert the majority of their biological effects through their interactions with specific PRs.³⁵ Testosterone-derived progestins also bind to the AR.³⁴ Both PRs³⁶ and ARs^{37, 38} have been identified in the kidney, suggesting that it is a target organ for these sex hormones and evaluation of RBA is a suitable method of determining the progestational and androgenic activity of the OC progestin. While this is the first study using progestational and androgenic RBA as a means of evaluating the effects of the OC progestin on renal hemodynamics, other investigators have used a similar method in human studies.²⁰

Animal studies support a positive relationship between progesterone levels and RAA System activity,^{18, 19, 39, 40} though few studies exist in humans. In postmenopausal women, addition of progesterone to estrogen therapy was associated with an increase in circulating components of the RAA System.⁴¹ In the low-salt state, increased endogenous serum progesterone concentrations in hypertensive, postmenopausal women are associated with a blunting of the BP and RVR response to infused Ang II, though these effects were abolished in high-salt balance.¹⁰ It is thus conceivable that the lack of association between progestational activity and change in PRA in our study is due to the fact that all of our

subjects were in the high-salt state. However, caution must be used in directly applying these findings regarding endogenous progesterone to synthetic progestin as there are clear structural and functional differences between the two compounds.⁴²

Androgens also stimulate synthesis and activity of the RAA System.^{43–45} In rats, PRA is positively correlated to testosterone levels^{8, 46, 47} and androgen levels predict angiotensin-dependent control of arterial BP.⁴⁸ Men demonstrate higher PRA levels compared to women,^{49, 50} and a sexual dimorphism has been noted in renal RAS activity.^{51, 52} Androgens play a crucial role in mediating renal injury and hypertension not only in men, but also in women in a physiological state of high androgen levels, such as menopause.⁵³ We are unaware of previous studies looking at the androgenic content of OCs and its effects at the level of the kidney, and one could hypothesize from the results of our study that increased RAA System activity associated with chronic exposure to high androgenic activity from the OC may be detrimental to renal function.

This study has limitations. First, we did not show an association between ethinyl estradiol content and activation of the RAA System in our study as has been previously shown,^{2, 3, 6, 54, 55} which may be a reflection of lack of power due to limited sample size and narrow range of ethinyl estradiol in the studied OC formulations. Second, the study sample was not from a target patient population in that participants were selected for normal BP, renal function, and urinalysis. By studying a homogeneous sample with stable ethinyl estradiol exposure, we hoped to examine the impact of the progestin component of the OC, without confounding factors. Third, while we included subjects with Type 1 diabetes, we controlled glycemic status throughout the study and exclusion of diabetic subjects did not alter the results. Previous studies have suggested that OC use has similar renal effects in both non-diabetic and diabetic OC users.^{3, 4, 6, 17} Fourth, we have used RPF response to captopril as a surrogate marker of renal RAA System activity in our study. While indirect, this approach is one of the few methods available for determining intrarenal RAA System in humans. The RPF response to ACE inhibition is highly correlated with angiotensin receptor blockade in both healthy⁵⁶ and diabetic⁵⁷ subjects. The lack of correlation between changes in BP or PRA and the RPF in response to captopril makes it extremely probable that the RPF response to ACE-inhibition reflects reversal of an increase in Ang II-mediated renal vascular tone. Fifth, while there are limited data on the pharmacokinetics of most progestins,⁵⁸ considerably more is known about testosterone-derived progestins (as used by all study subjects) with the majority of data obtained from studies in which the progestin was a component of an OC formulation.⁵⁸ Finally, while similar to that of other human studies examining the hemodynamic effects of the OC^{2, 3, 59–61}, our sample size was limited, though this effect was minimized by ensuring all subjects were ingesting similar amounts of salt to minimize RAA System activation.

In our study, women ingesting OCs with higher progestational and androgenic activity demonstrated increased angiotensin-dependent control of the renal circulation, suggesting a role for OC progestins as a determinant of renal RAA System activity. While larger, confirmatory studies are needed prior to recommending changes to clinical practice, the findings of this study merit attention given the strong association between RAA System activity and nephropathy.

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Society for Clinical Investigation Annual Meeting in Toronto, Ontario, Canada in September 2008 and the American Society of Nephrology Annual Meeting in Philadelphia, Pennsylvania, USA in November 2008.

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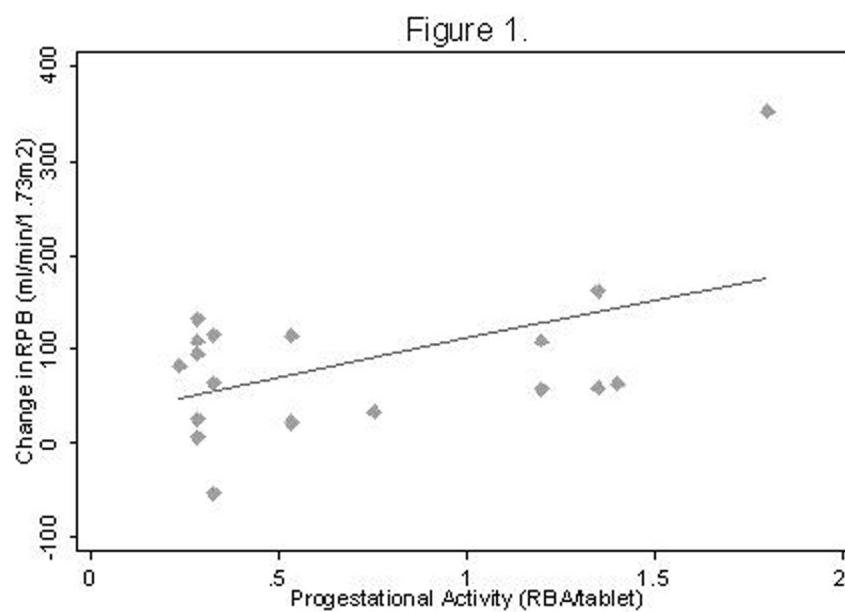


Figure 1. RPF response to ACE-inhibition as a function of progesterone activity

R = 0.52, P = 0.03, N = 18

Abbreviations: RPF, renal plasma flow; ACE, angiotensin converting enzyme; RBA, receptor binding affinity

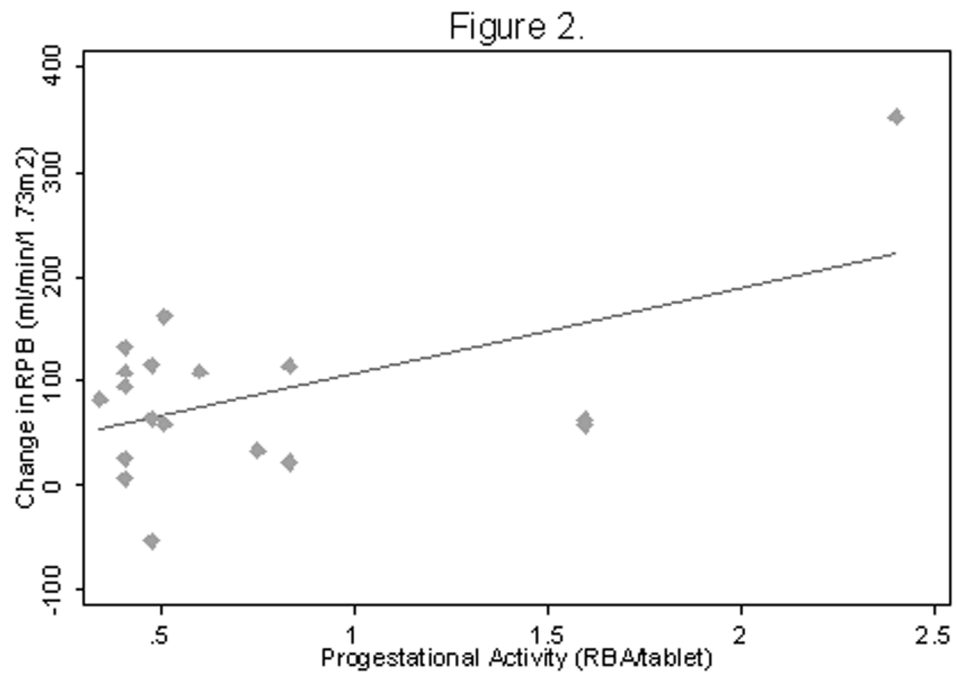


Figure 2. RPF response to ACE-inhibition as a function of androgenic activity

$R = 0.54$, $P = 0.02$, $N = 18$

Abbreviations: RPF, renal plasma flow; ACE, angiotensin converting enzyme; RBA, receptor binding affinity

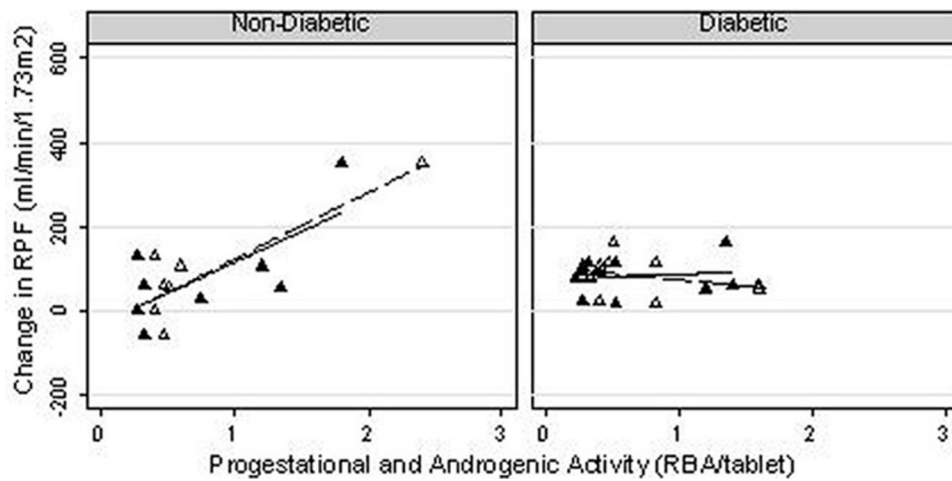


Figure 3. Renal plasma flow response to ACE-inhibition as a function of progestational and androgenic activity of the OC progestin, by diabetic status

▲ Progestational Activity

△ Androgenic Activity

— Progestational Activity

--- Androgenic Activity

Non-Diabetics:

Progestational Activity: $R=0.71$, $p=0.05$; Androgenic Activity: $R=0.88$, $p=0.005$

Diabetics:

Progestational Activity: $R=0.14$, $p=0.7$; Androgenic Activity: $R= -0.33$, $p=0.3$

Table 1Baseline Characteristics^{*}

	All Subjects (n=18)	Non-Diabetic (n=8)	Diabetic (n=10)
Age (years)	23±4	23±3	23±5
Smoker n (%)	3 (17)	1 (13)	2 (20)
BMI (kg/m ²)	25±4	25±6	25±3
MAP (mmHg) [†]	83±6	84±5	83±6
Duration of Diabetes (years)	-	-	9.8±4.1
Hemoglobin A1c (%)	-	-	7.6±1.7
Ethinyl estradiol (µg/tablet)	32±5	33±3	31±6
Progestin (mg/tablet)	0.43±0.42	0.54±0.49	0.34±0.35
Progestational Activity (RBA)	0.71±0.52	0.79±0.59	0.64±0.48
Androgenic Activity (RBA)	0.75±0.56	0.75±0.67	0.74±0.48
PRA (ng Ang I/mL/h)	0.5±0.45	0.5±0.36	0.6±0.53
Fasting Serum Glucose (mg/dL) (mmol/L)	122±67 (6.8±3.7)	80±5 (4.4±0.3)	151±78 (8.4±4.3)
Urine Sodium (mmol/24h)	276±89	282±83	272±98
RPF (ml/min/1.73m ²) [†]	614±73	646±81	588±57
RVR (mmHg/mL/min/1.73m ²)	85±11	81±11	88±10

Abbreviations: BMI, body mass index; MAP, mean arterial pressure; PRA, plasma rennin activity; Ang I, angiotensin I; RPF, renal plasma flow

^{*} Data are expressed as mean ± standard deviation unless otherwise indicated

[†] Median of readings at t = -10 min, -5 min and 0

Table 2

Progestin component of oral contraceptive, by subject

Non-Diabetic Subjects		Diabetic Subjects	
Progestin Type	Dose	Progestin Type	Dose
Desogestrel *	0.15 mg	Desogestrel *	0.15 mg
Norethindrone *	0.75 mg	Ethynodiol diacetate *	1 mg
Norethindrone *	1.5 mg	Levonorgestrel *	0.1 mg
Norethindrone acetate *	1 mg	Levonorgestrel *	0.1 mg
Norgestimate *	0.215 mg	Norethindrone *	1 mg
Norgestimate *	0.215 mg	Norgestimate *	0.18 mg
Norgestimate *	0.25 mg	Norgestimate *	0.215 mg
Norgestimate *	0.25 mg	Norgestimate *	0.215 mg
		Norgestimate *	0.215 mg
		Norgestimate *	0.25 mg

* Structurally related to testosterone

Table 3

Response to angiotensin-converting enzyme inhibition *

	All Subjects (n=18)	Non-Diabetic (n=8)	Diabetic (n=10)
MAP Nadir (mmHg) [†]	78±7 [§]	81±6 [§]	76±7 [§]
ΔMAP (mmHg)	-5±7	-3±5	-7±8
Peak PRA (ng Ang I/mL/h)	1.9±2.4 [§]	2.6±3.4 [§]	1.5±1.3 [§]
ΔPRA (ng Ang I/mL/h)	1.4±2.2	2.1±3.1	0.9±1.0
Peak RPF (ml/min/1.73m ²) [‡]	699±123 [§]	733±152 [§]	672±94 [§]
ΔRPF (ml/min/1.73m ²)	85±85	87±122	84±44
Nadir RVR (mmHg/mL/min/1.73m ²)	70±11 [§]	70±16 [§]	69±11 [§]
ΔRVR (mmHg/mL/min/1.73m ²)	-15±9	-11±9	-18±7

Abbreviations: MAP, mean arterial pressure; PRA, plasma renin activity; Ang I, angiotensin I; RPF, renal plasma flow.

* Data are expressed as mean ± standard deviation unless otherwise indicated

[†] Mean of 2 readings at nadir of response to captopril[‡] Mean of 2 readings at peak response to captopril[§] p<0.05 compared to baseline

Table 4**Summary Table**

What is known about topic	<ul style="list-style-type: none"> • Oral contraceptive use is associated with increased intrarenal RAS activity and risk of nephropathy • Progestins in the oral contraceptive have been associated with increased blood pressure, albuminuria and loss of kidney function by an unclear mechanism • The role of progestins in the oral contraceptive in activation of the RAA System is unknown
What this study adds	<ul style="list-style-type: none"> • Progestational activity of the oral contraceptive predicts degree of intrarenal RAA System activity • Androgenic activity of the oral contraceptive predicts degree of intrarenal RAA System activity • Given the strong association between RAA System activity and kidney disease, women at risk of nephropathy may wish to consider oral contraceptives with low progestational and androgenic activity